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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/028,395	02/24/98	PROCKOP D	9598-32

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KATHRYN DOYLE LEARY
PANITCH SCHWARZE JACOBS & NADEL
ONE COMMERCE SQUARE
2005 MARKET SQUARE 22ND FLOOR
PHILADELPHIA PA 19103-7086

EXAMINER	
KERR, J	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/028,395	Applicant(s) PROCKOP ET AL.	
	Examiner Janet Kerr	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13,14* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Response to Arguments

Applicants' request for reconsideration, filed 11/27/00, has been entered.

Claims 1-20 remain pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record and the reasons below.

The claims are directed to methods of treating a human patient having a disease, disorder or condition of the central nervous system (CNS) comprising obtaining a bone marrow sample from a human donor, isolating stromal cells from the bone marrow, and administering the isolated stromal cells to the CNS of the patient. The disease, disorder, or condition can be a genetic defect disease, a tumor, i.e., a brain tumor, trauma, stroke, or injury to the tissues or cells of the CNS. The cells can be transfected with an isolated nucleic acid encoding a therapeutic protein, which can be a cytokine, a chemokine or a neurotrophin. The nucleic acid can be a wild type copy of a mutated, non-functioning or under-expressed gene. The isolated stromal cells can be immunologically isolated.

As stated in the office actions of 10/4/99 (Paper No. 6) and 5/24/00 (Paper No. 12), the specification is non-enabling for the claimed methods as the specification does not provide sufficient guidance as to how one of skill in the art would treat a human patient having a disease, disorder, or condition of the CNS by administering isolated stromal cells from a human donor. The specification does not disclose any specific disease, disorder, or condition of the CNS which

has been subjected to the claim-designated treatment regimen, nor does the specification disclose any specific methodology associated with such a treatment regimen including the number of cells to be administered for each disease, disorder, or condition, the route of administration for each disease, disorder, or condition, or the relevant cell therapy target site for the specific disease, disorder, or condition of the CNS. Furthermore, the specification does not disclose how to immunologically isolate the cells to treat a specific disease, disorder, or condition of the CNS. In addition, the state of the art at the time of filing teaches that mesenchymal stem cell transplantation and in vivo therapeutic effectiveness is neither routine nor predictable.

Applicant's arguments filed 11/27/00 have been fully considered but they are not persuasive.

It is argued that reliance on the Prockop reference is improper as the Prockop reference (D. J. Prockop, Science, 276:71-74, April, 1997), which is not a "prior art" reference, is not a post-filing date reference for purposes of 35 U.S.C. 112, first paragraph (see page 3 of applicants' Remarks). This is not persuasive. Regardless of the publication date of the Prockop reference, the reference was relied upon as one of several references as evidence that the state of the art, at the time of filing, of using mesenchymal stem cells in therapeutic regimens, is neither routine nor predictable. As stated in the previous office action, the author of the reference, D. J. Prockop, who is also a co-inventor of the instant application, clearly recognizes that utilization of mesenchymal stem cells (MSCs) in cell and gene therapy is neither routine nor predictable.

It is asserted that (1) the claimed cell and gene therapy methods are enabled by the specification given the teachings in the specification, (2) that applicants need not have actually reduced the invention to practice prior to filing, and (3) that the invention need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without undue amount of experimentation. Applicants rely on MPEP § 2164.01, 2164.02, and 2164.05(a) and case law cited therein, to argue that applicant need not have actually reduced the invention to practice prior to filing, that the invention need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be

able to practice it without an undue amount of experimentation, that the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue, that while experimentation may be complex, it does not necessarily make it undue if the art typically engages in such experimentation, and that the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public.

These arguments are not persuasive. As stated in the MPEP § 2164.01(a), there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue", the factors including, the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The pending claims are directed to methods of treating a human patient having a disease, disorder or condition of the central nervous system (CNS) comprising obtaining a bone marrow sample from a human donor, isolating stromal cells from the bone marrow, and administering the isolated stromal cells to the CNS of the patient. The disease, disorder, or condition can be a genetic defect disease, a tumor, i.e., a brain tumor, trauma, stroke, or injury to the tissues or cells of the CNS. The cells can be transfected with an isolated nucleic acid encoding a therapeutic protein, which can be a cytokine, a chemokine or a neurotrophin. The nucleic acid can be a wild type copy of a mutated, non-functioning or under-expressed gene. The isolated stromal cells can be immunologically isolated.

The nature of the invention is directed to treatment of a patient having a disease, disorder or condition of the CNS. The claims are extremely broad in that the patient can have any disease, disorder or condition of the CNS, and the method step merely requires administration of isolated stromal cells obtained from the patient. The cells can be transfected with a nucleic acid encoding

a therapeutic protein such as a cytokine, chemokine or neurotrophin and the nucleic can be a wild type copy of any mutated, non-functioning or under-expressed gene. Although applicants argue that the specification provides ample direction for practicing the claimed invention, as set forth in the office action of 10/4/99, the specification broadly discloses different diseases, conditions, and disorders which can be treated by cell therapy, and broadly discloses *ex vivo* gene therapy strategies for treating the diseases, conditions or disorders of the CNS. As stated above, and in the previous office actions, with regard to cell therapy, there is no correlation between treatment of a specific disease and the methodology required such that the treatment is achieved. For example, the specification does not disclose any specific disease, disorder, or condition of the CNS which has been subjected to the claim-designated treatment regimen, including the number of cells required to treat a particular disease, disorder, or condition, the route of administration of the cells necessary to treat a particular disease, disorder, or condition, or the relevant cell therapy target site for the specific disease, disorder, or condition. With regard to *ex vivo* gene therapy, the specification only discloses isolated mesenchymal stem cells which have been transfected with a retroviral vector comprising collagen promoters operatively linked to a reporter gene. There is no disclosure in the specification of vector constructs comprising nucleic acid sequences encoding therapeutic proteins, in general, or cytokines, chemokines, or neurotrophins which when transfected into the cells which are subsequently administered to a patient, would have therapeutic effectiveness in treating a patient with a CNS disease, disorder, or condition. There is no correlation between a mutated, non-functional, or under-expressed gene and a CNS disease, disorder, or condition, or whether *ex vivo* gene therapy would be effective in overcoming the disease, disorder, or condition whose etiology stems from a mutated, non-functional, or under-expressed gene. Clearly, the specification does not provide sufficient guidance as to how to practice the invention as claimed.

With respect to the state of the art regarding cell and *ex vivo* gene therapy, the teachings of Prockop, Gerson, Sanberg *et al.*, and Sabate *et al.* provide ample evidence that at the time of filing, cell and ex vivo gene therapy protocols directed to treating CNS diseases, disorders, or

conditions is neither routine nor predictable (see pages 3-5 of the Office action of 10/4/99). Prockop (1997) cautions that although different strategies are being pursued for therapeutic use of MSCs and that a phase I clinical trial has demonstrated that systemic infusion of autologous MSCs appears to be well tolerated, a number of fundamental questions about MSCs still need to be resolved before they can be used for safe and effective cell and gene therapy. With respect to cell therapies for treating CNS disorders, Sanberg *et al.* (1998) indicate that it is difficult to treat conditions which involve multiple neuron populations and extensive cell death throughout the brain using cell transplantation. With respect to gene therapy regimens for treating a CNS disease, disorder, or condition, Sabate *et al.* (1996) teach that there are several important issues to be resolved if gene therapy for neurological diseases is to become a reality including (1) extent of transgene expression, (2) stability of transgene expression, (3) targeting of the cells, and (4) safety of the procedure. In a 1999 publication, Gerson indicates that many questions need to be addressed regarding the utilization of MSCs in therapeutic regimens including (a) what is the minimal proportion of donor MSCs required to affect a long-lasting therapeutic response?, (b) to which host tissues do infused MSCs home, proliferate, and differentiate, and using which regulatory signals?, © can MSCs be used effectively for gene transfer and gene deliver?, (d) is systemic infusion optimal or is infusion into a target organ required?. Based on the teachings in the references, the examiner has provided ample evidence that the state of the art with respect to cell and gene therapy techniques is neither routine nor predictable.

Section 2164.03 of the MPEP states that the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is , the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is

unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.

In view of the breadth of the claims, the lack of sufficient guidance in the specification as to how to practice the invention commensurate in scope with the claims, the lack of a working example directed to the claimed invention, and unpredictability in the art with regard to cell and gene therapy directed to treating a person with a CNS disease, disorder, or condition, applicants' arguments that the claimed cell and gene therapy methods are enabled given the teachings in the specification, that the specification provides an extensive disclosure concerning how the presence of MSCs effects treatment further supports that one skilled in the art, and that armed with the teachings of the instant invention and the knowledge of the prior art, the artisan would be able to determine without undue experimentation what diseases, disorders or conditions of the CNS are suitable for treatment by administering isolated stromal cells is not persuasive.

Applicants argue that the teachings of Horwitz *et al.* and Schwartz *et al.* demonstrate the high degree of skill in the art, the extensiveness of the experimentation routinely performed by the artisan, and that one skilled in the art of gene and cell therapy typically engaged in this type of experimentation at the time the application was filed (see page 5, second full paragraph of applicants' Remarks).

These arguments are not persuasive. Initially, it is noted that both references are post-filing references (1999). As has been previously discussed, the reference of Horwitz *et al.* (1999) is directed to the therapeutic effects of marrow-derived mesenchymal cell administration to children suffering from osteogenesis imperfecta. The disease condition treated in this reference is not relevant to applicants' claimed invention. This reference does not disclose any particular CNS disorder, condition, or disease, nor does the reference provide any guidance with respect to how to treat a CNS disorder, condition, or disease. With regard to the Schwartz *et al.* reference, the reference teaches that the introduction and expression of two genes, TH and GC, in MSCs, and the implantation of a specified amount of cells, in a particular area in the brain are required to achieve therapeutic effectiveness in the rat model of Parkinson's disease. There is no disclosure in

the instant application of transducing MSCs with these genes, the method of administration of the MSCs, or any treatment effect in humans as a result of the administration. The teachings in the specification would not have led one of skill in the art to make and use the invention taught in the post-filing reference of Schwartz *et al.* Moreover, it is noted that Schwartz *et al.* teach that the therapeutic effect initially observed after engraftment of the MSCs is no longer present after 14 days as the expression of the transgenes is lost (see, e.g., page 2544, left column). One of skill in the art at the time of filing would not have recognized, *a priori*, that two distinct exogenous genes are required to produce a therapeutic effect, nor would the skilled artisan have recognized that expression of the genes, and therefore, the treatment efficacy would have been extremely transient. In addition, the experiments described by Schwartz *et al.* are directed to a particular disease state in which a particular animal model system for studying the disease state has been established. There is no suggestion in the reference of Schwartz et al that the model system and the method of treatment can be applied to the broadly claimed CNS diseases, disorders, or conditions affecting a human patient.

With regard to applicants argument that generic claims reciting large numbers of species are allowable without disclosure of every species so long as the art engages in experimentation to identify the operative species encompassed by the generic claim (see pages 5-10 of applicants' Remarks), it is noted that applicants have not provided any identification of an operative species encompassed by the generic claim. The only operative example provided in the specification is directed to implantation of MSCs in a specific area in the brain of rats, not treatment of a CNS disease, disorder, or condition. Section 2164.03 of the MPEP states that the scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. This is because it is not obvious from the disclosure of one species, what

other species will work. With regard to treatment of CNS diseases, disorders, or conditions, the specification only broadly discloses that a myriad of CNS diseases, disorders, or conditions can be treated by mere administration of MSCs, or administration of MSCs that have been transfected with non-disclosed cytokines, chemokines or neurotrophins. As stated above and in the previous office actions, one of skill in the art could not practice the invention as claimed without undue experimentation given the lack of guidance in the specification, the lack of a working example directed to the claimed invention, and the state of the art and the unpredictability in the art at the time of filing. Thus, applicants' argument is not persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19 and 20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Eglitis *et al.*, taken with Pereira *et al.*, Friedmann, and Prockop for the reasons of record and the reasons below.

Applicant's arguments filed 11/27/00 have been fully considered but they are not persuasive.

Applicants argue that the prior art references relied upon do not teach the claimed limitations, nor is there any suggestion to combine the references.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Prockop teaches that directing differentiation of marrow-derived cells into a variety of cell types is known in the art. Friedmann teaches that marrow contains cells which can be directed to differentiate into central nervous system-associated cell types. Eglitis *et al.* and Pereira *et al.* teach that *in vivo* administration of marrow-derived cells results in the differentiation of the marrow-derived cells into different lineages depending on which tissue is repopulated. In view of the teachings of Eglitis *et al.* that the identity of the majority of bone marrow-derived cells remains an open question, one of skill in the art would have been motivated to establish cell culture conditions which allow the identification of bone marrow-derived cells, and which would allow the identification of the microenvironment required to recapitulate the *in vivo* observations of Eglitis *et al.* and Pereira *et al.* As culturing of MSCs is known in the art, and in view of the above teachings that the differentiation of MSCs in vivo is dependent on the microenvironment of the cells, co-culturing of cells of the neural lineage, e.g., astrocytes, with MSCs, to establish the microenvironment required to differentiate MSCs into the appropriate lineage, would have been obvious and well within the purview of one of ordinary skill in the art. Thus, the rejections are maintained.

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to Deborah Clark, Supervisory Primary Examiner of Art Unit 1633, at (703) 305-4051. Any administrative or procedural questions should be directed to Kimberly Davis, Patent Analyst, at (703) 305-3015. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401.

Janet M. Kerr, Ph.D.
Patent Examiner
Group 1600

DEBORAH J. R. CLARK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600